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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/756,690	01/09/2001	Orville G. Kolterman	030639.0066.UTL	4666

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EXAMINER	
JIANG, DONG	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 11/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/756,690	KOLTERMAN ET AL.	
	Examiner	Art Unit	
	Dong Jiang	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 August 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15,24-37 and 41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15,24-37 and 41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED OFFICE ACTION

Applicant's response filed on 19 August 2004 is acknowledged.

Currently, claims 1-18 and 24-41 are pending, and claims 1-15, 24-37 and 41 are under consideration.

Withdrawal of Objections and Rejections:

The rejection of claims 1-15, 24-37 and 41 for lack of enablement under 35 U.S.C. 112, first paragraph, is withdrawn in view of applicant's argument.

Objections and Rejections under 35 U.S.C. 112:

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-15, 24-37 and 41 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for claims limited in scope to a method for lowering triglyceride levels in a subject having diabetes, does not reasonably provide enablement for claims to a method for lowering triglyceride levels in any subject in need thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The present claims are directed to a method for lowering triglyceride levels with an exendin in a subject having elevated postprandial triglyceride levels, which reads on any or all subjects having elevated postprandial triglyceride levels. In the example relied upon, Example 186 of the specification, only patients with type 2 diabetes were treated with exendin-4, and as a

result, postprandial circulating triglycerides, plasma glucose, and glucagon were significantly reduced. Such treatment of diabetic patients would be proper and beneficial since both blood glucose and triglycerides levels are elevated, and contribute to the development of the disease, and exendin-4 is known to lower both levels. However, such treatment would not be suitable for non-diabetic subjects merely having elevated postprandial triglyceride levels because an exendin, would inherently lower the blood glucose levels, which would be dangerous for the treated subject whose blood glucose levels are not elevated. Further, the present specification (at page 149) indicates that hypoglycemia is one of the most frequent adverse event. Therefore, it is not predictable whether any or all subjects having elevated postprandial triglyceride levels are suitable for the treatment with an exendin, which has a primary role in lowering blood glucose levels. The art has not established such, and the specification provides no guidance or working example as to how to treat a patient other than a diabetic with elevated postprandial triglyceride levels. Therefore, in the absence of supporting evidence that an exendin, a hypoglycemic agent, can be used for treating non-diabetic patients with elevated postprandial triglyceride levels, [undue experimentation would be required in order to determine if the claimed method could be practiced on non-diabetics, and if so, how it should be practiced and what guideline should be followed, which is, by no means, considered by a skilled in the art a routine experimentation.

Due to the large quantity of experimentation necessary to determine whether an exendin is suitable for treating non-diabetic patients with elevated postprandial triglyceride levels, and how to apply the exendin to such patients, the lack of direction/guidance presented in the specification regarding same, the absence of working examples directed to same, the complex nature of the invention as an exendin would lower both blood glucose and triglyceride levels, the state of the prior art, which has not established that an exendin capable of lowering both glucose and triglyceride levels is suitable for non-diabetic patients without elevated glucose levels, and the breadth of the claims which embrace a broad class of subjects with or without elevated glucose levels, undue experimentation would be required of the skilled artisan to use the claimed invention in its full scope.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-14, 24-36 and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Karpe et al. (Metabolism, 1999, 48:301-307), and in view of Beeley et al. (WO 98/30231), as applied to the rejection of the same claims in the previous Office Action, paper No. 25, mailed on 10 April 2003, and Beers et al. (the Merck Manual, 1999, 17th edition, pages 200 and 2550).

Karpe discloses that the postprandial elevation of plasma triglycerides is more closely linked to coronary heart disease (CHD) than the fasting level, and that the plasma triglyceride concentration measured 6 hours after a mixed meal was associated with signs of early atherosclerosis in healthy men (page 301, the second paragraph of the left column; and page 306, the last paragraph of the right column). Karpe does not teach a method for lowering triglyceride levels with an exendin.

The teachings of Beeley were reviewed in the previous Office Action (paper No. 25). Beeley teaches a method of treatment by administering an exendin or an agonist thereof, which can be used for conditions or disorders such as obesity, diabetes, eating disorder, and insulin-resistance syndrome, for *lowering plasma lipids*, and for reducing the cardiac risk (page 10, lines 4-19).

Further, as addressed in the previous Office Action, it is well established in the art, and evidenced by Beers that the triglycerides are *major* plasma lipids, which also include cholesterol. As such, Beeley's method for lowering plasma lipids would inherently lower the triglyceride levels. Additionally, it is further evidenced by Beers that diabetes has increased triglyceride

levels (page 2550, Table 296-4). Therefore, Beeley's method of treating diabetes with an exendin would inherently lower the triglyceride levels.

Therefore, it would have been obvious to the person of ordinary skill in the art at the time the invention was made to treat a patient having elevated triglyceride levels by administering an exendin or an agonist thereof following the method taught by Beeley in order to lower the triglyceride levels, wherein the patient would be identified by his elevated postprandial triglyceride levels following the teachings of Karpe. The person of ordinary skill in the art would have been motivated to do so in order to treat and reduce the risk of CHD, and because the postprandial elevation of plasma triglycerides is more closely linked to CHD as taught by Karp, and reasonably would have expected success because Beeley has taught that an exedin can lower plasma lipids, and Karpe has demonstrated that the postprandial elevation of plasma triglycerides is more closely linked to CHD, and is also indicative for early atherosclerosis, in contrast to fasting plasma triglycerides.

Claims 15 and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Karpe et al. (Metabolism, 1999, 48:301-307), Beeley et al. (WO 98/30231), and Beers et al. (the Merck Manual, 1999, 17th edition, pages 200 and 2550), as applied to claims 1-14, 24-36 and 41 above, and further in view of Wagle et al., US 6,326,396 B1.

The teachings of Karpe, Beeley and Beers are reviewed above. None of the three references teaches to use an exendin or an exendin agonist in combination with a statin.

The teachings of Wagle were reviewed in the previous Office Action (paper No. 25), and reiterated below.

Wagle teaches that HMG-CoA reductase inhibitors (also known as "statins") are agents acting directly on plasma triglyceride and cholesterol content, and are effective in lowering triglyceride and cholesterol content, and that lowering of circulating lipids has been to reduce the cardiovascular morbidity (column 2, lines 28-33).

It would have been prima facie obvious to one of ordinary skill in the art to combine the teachings of the references and to combine an exendin or an exendin agonist with a statin (HMG-CoA reductase inhibitor) for lowering plasma lipid levels because each of the two drugs is well known for its effect on lowering plasma lipid. The instant situation is amenable to the type of

analysis set forth in *In re Kerkhoven*, 205 USPQ 1069 (CCPA 1980) wherein the court held that it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to form a third composition that is to be used for the very same purpose since the idea of combining them flows logically from their having been individually taught in the prior art. Applying the same logic to the instant method claims, given the teaching of the prior art of methods using exendins or exendin agonists, or statins for lowering plasma lipids or treating diabetes, it would have been obvious to combine the two drugs for lowering plasma triglyceride and cholesterol because the idea of doing so would have logically followed from their having been individually taught in the prior art to be useful for the same purpose of lowering plasma lipid. Thus, claims that require no more than adding together of two conventional drugs set forth prima facie obvious subject matter. The person of ordinary skill in the art would have been motivated to do so because Wagle teaches that lowering plasma triglyceride and cholesterol is beneficial for reducing the cardiovascular morbidity, and reasonably would have expected success because both drugs had been demonstrated in the prior art to be effective on lowering plasma lipid.

Conclusion:

No claim is allowed.

Advisory Information:

Any inquiry concerning this communication should be directed to Dong Jiang whose telephone number is 571-272-0872. The examiner can normally be reached on Monday - Friday from 9:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback, can be reached on 571-272-0961. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

LORRAINE SPECTOR
PRIMARY EXAMINER

Dong Jiang, Ph.D.
Patent Examiner
AU1646
11/5/04